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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KIM, VICKIE Y

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/856,352	Applicant(s) FISCHER, PETER	
	Examiner Vickie Kim	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 7-13 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7-13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Applicant's arguments filed October 22, 2002 have been fully considered but they are not persuasive. However, applicant's arguments with respect to claims 1-6 have been considered but are moot in view of the new ground(s) of rejection. It is noted that the new ground(s) of rejection is added due to the changes made in scope of the claims wherein the instant claims 7-13 are now directed to the method of treating delirium using anticholinesterase inhibitors. The original claims 1-6 were drawn to the use of the effectors of the cholinergic central nervous system.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. > Will be cancelled

Claim 9 recites the further limitation "cause by anticholinergic intoxication ". However, claim 7 excludes anticholinergic intoxication from the possible causative factors. There is insufficient antecedent basis for this limitation in the claim. To be consistent to the scope of previous claim, this examiner will continue the examination without considering this said limitation, thus the further limitation recited in claim 9 is withdrawn from the consideration because it is meaningless, but the claim 9 will be

considered and included in the examination based on the same scope(limitation) recited in the claim 7.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 7-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Rupreht et al(1990, abstract only).

Claims 7-11 are drawn to the method of treating delirium which is a postoperative delirium or, cause by substance withdrawal or a hypoglycemic process, but neither by anticholinergic intoxication nor by degeneration of cholinergic system using acetylcholine esterase inhibitors.

Rupreht et al teach the central anticholinergic syndrome(CAS) such as confusion or delirium which is occurred during postoperative period, and caused by overdoses of both anticholinergic medication(e.g. atropine), non-anticholinergic medication(e.g. opioids, halothane, benzodiazepine, anaesthetics), and hypoglycemia. Rupreht further teaches that CAS as a result if an insufficient release of acetylcholine can be effectively treated by a therapeutically effective aceticholinesterase inhibitor, Physostigmine, see entire abstract. All the critical elements are taught by the cited reference and the claimed subject matter is not patentably distinct over the prior art of the record.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rupreht et al(1990, abstract only) alone.

Rupreht et al's teaching is mentioned in 102 rejection(supra).

Even though Rupreht et al have not mentioned about hypoglycemic coma or resuscitation as the causative factor, it would have been obvious to one of ordinary skill in the art at the time of invention made to extend Rupreht et al's teaching of acetylcholinesterase inhibitor administration for treating delirium or confusion caused by hypoglycemic coma and resuscitation because Rupreht et al's teaching suggests that CAS(e.g. delirium, confusion) caused by inadequate acetylcholine release would be effectively treated by acetylcholinesterase inhibitor and it also suggests that acetycholinesterase inhibitior treatment should be performed before any diagnosis of CAS with exclusion. One would have motivated to so, with reasonable expectation of success, because Rupreh's teaching(i.e. acetylchoinesterase inhibitor treatment) includes hypoglycemia which encompasses hypoglycemic coma and neurological damages or hypoxia where it is well known in the art that improper resuscitation often causes neurological damages or hypoxia, .absent evidence to the contrary.

6. Claims 7-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Enz(US 5,602,176) in view of Oshiro et al (US 5,556,857).

US '176 teaches a method of treating acute confusion disorders using a pharmaceutical composition comprising a therapeutically effective amount of (s)-N-

ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenylcarbamate (rivastigmine:chemical name, used hereafter);see column 5, lines 1-3. US'176 also teaches that rivastigmine is acetylcholinesterase inhibitor; see column 1. It also noted that the term "delirium" is a synonym of "acute confusion disorder" as admitted in instant application; see instant specification at page 4, second paragraph(lines 25-27).

However Enz is silent about the etiologyies(causative factors) of acute confusion disorder(delirium).

Oshiro et al(US'857) teaches that disturbance of consciousness including delirium and confusion are associated with various causes including primary lesion(e.g. brain surgery, head injury) or secondary lesion(e.g. metabolic disorders including hypoglycemia, poisoning by drugs such as hypnotics or psychotropic drugs, alcoholism, liver damage, coma, cardiac arrest, etc). Oshire et al teach that delirium or confusion is developed in chronic stages (see column 1, line 67-column 2, line 1) which is resulted from altered brain function and can be effectively treated via acetylcholine activation by administration of acetylcholinesterase inhibitor such as physostigmine. It also states that external stimuli inhibits the acetylcholinergic nervous system, thus causing a decreased level if consciousness; see column 1, lines 20 thru column 2, lines 35.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to select cholinergic CNS effectors (i.e. acetylcholinesterase inhibitor(e.g. rivastigmine)) suggested by Enz to treat delirium(acute confusion disorder) including both anticholinergic and non-anticholinergic because Oshiro suggests that acetylcholinergic nervous system activators would be effective for treating

any delirium(impaired consciousness) that could be caused by not only cholinergic but also non-anticholinergic factors such as sustanace poisoning(equivalent term with intoxication), alcoholism, hypoglycemia , a metabolic disorders (e.g.liver damage, cardiac arrest and so on), postoperation (e.g. surgery) or others. In respect to claim 5 and claim 6, they are properly included in this rejection because Enz or Oshire teaches delirium(acute confusion disorder) in general not excluding any specific causes wherein one would expect the reasonable expectation of same therapeutic results to delirium therapy caused by resuscitation. It also would have been obvious to one having ordinary skill in the art to apply the same treatment to treat alcohol withdrawal symptoms when the treatment is effectively used in alcoholism treatment.

One would have been motivated to treat non-anticholinergic delirium by administering effectors of cholinergic CNS, with reasonable expectation of success, because deactivation of cholinergic nervous system is biological mechanism for inducing delirium wherein cholinergic CNS effectors (e.g. acertylcholinesterase inhibitors or acetylcholinergic receptor agonists) is a primary source and it effectively and directly activates cholinergic nervous system and improves the delirium(acute confusion disorder) as suggested by each cited reference.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same (or similar) ingredients and share common utilities, and pertinent to the problem which applicant is concerning. MPEP 2141.01(a).

Response to applicant's argument: In applicant's traverse, (at page 5, last paragraph), applicant states that ENZ is directed to a cholinesterase inhibitor (emphasis added by underline), phenyl carbamate. This examiner would like to point out that the phenyl carbamates including(s)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenylcarbamate (rivastigmine:chemical name) is acetylcholinesterase inhibitor as specifically mentioned throughout the text(see, for example, column 1, lines 57 and 61). In applicant's traverse, applicant allegedly states that ENZ's teaching is directed to the anticholinergic related disorders thus ENZ's teaching is not related to present invention (see page 6, last two lines of first paragraph). This examiner is not sure what applicant means by anticholinergic related disorders. Is it the diseases caused by intoxication of anticholinergic drugs? This examiner would like to request where is the support for the said allegation? In any event, This examiner, as mentioned above in 103 rejection, ENZ fails to teach the etiologies (causative factors) of the diseases stated in the patent. Therefore, this examiner is arrived in conclusion that one of ordinary skill in the art to apply conventional wisdom wherein one would utilize acetylcholinesterase inhibitor to treat acute confusion which derived from inhibited acetylcholinergic nervous system regardless causes so that reactivation of acetylcholinergic nervous system by acetylcholinesterase inhibitor would effectively treat the acute confusion. This examiner adopt the Oshiro's teaching because the possible causative factors are taught and suggested by Oshiro where Oshire also teaches very same biological pathway of ENZ (i.e acetylcholinergic nervous system) and further teaches that the causative factors taught in his patent inhibit the acetylcholine nervous system(see column 2).

Conclusion

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vickie Kim whose telephone number is 703-305-1675. The examiner can normally be reached on Tuesday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on 703-308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-3165 for regular communications and 703-746-3165 for After Final communications. Any inquiry of a general nature or

relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Vickie Kim,

Patent examiner

March 7, 2003

Art unit 1614

William Jarvis

Primary Patent examiner